Mastitis and Retained Placenta - Relationship to Bovine Immunology and Nutrition

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- **Take Home Message**

  **Maintaining a Strong Immune System**

  At calving all cows white blood cells show a decreased ability to fight off infections which increases the susceptibility to mastitis and uterine infections. In part the immune suppression is thought to be due to changes in hormones at calving. However better nutrition can also strengthen the immune system at this time.

  - Prevent energy and protein deficiency - the effect of energy deficit on the immune function is, in my opinion, greatly underrated!
  - Feed adequate selenium
  - Feed vitamin E to animals without access to pasture.
  - Prevent milk fever
  - Supply trace minerals at 20 - 50% above NRC recommendations to account for decline in dry matter intake that accompanies calving.

  **Payoff** - Less mastitis, retained placenta (enhancement of neutrophil attack on fetal tissues!) and uterine infection.

  In addition to metabolic disease, the overwhelming majority of infectious diseases, especially mastitis, but also diseases such as Johne's disease and Salmonellosis, become clinically apparent during the first 2 wk of lactation.

  Two common diseases that seem to be related to immune suppression at calving are mastitis and retained placenta. These are discussed below along with some general nutritional strategies that may help reduce the degree of immune suppression experienced by the periparturient cow.
- **Mastitis**

A high proportion of new intramammary infections occur during the first wk of the dry period when milk flow ceases to flush bacterial invaders from the teat canal and before the gland is fully involuted (23, 24). However, these infections often do not result in clinical mastitis. While the immune cells eliminate many of these infections during the dry period, some are simply held in check until lactation begins. Clinical mastitis is most likely to occur during the first month of lactation, especially coliform mastitis (6, 23, 24), and is often the result of infection established during the dry period or during early lactation. This raises two important questions. Why do subclinical mammary infections obtained early in the dry period become clinical mastitis infections in early lactation, and why is the fresh cow’s udder so susceptible to infection? At least part of the answer is that the activity of the immune system of the cow is depressed during the wk before and after calving. Neutrophils obtained from cows during the first wk of lactation exhibit impaired ability to ingest and kill bacteria (19, 20, 22). The ability of lymphocytes to respond to mitogens and to produce antibody is also impaired around parturition (16, 18, 19, 20, 21, 33). The serum concentration of other components of the immune system such as immunoglobulin, complement, and conglutinin are also decreased at parturition in dairy cows (21, 27).

Intramammary infections held in check during the dry period can overcome the weakened immune system to become clinical mastitis cases at parturition. Coupled with the recrudescence of existing infections, the gland is also at increased risk of new infection around the time of parturition. As the mammary secretions change over to colostrum, the level of lactoferrin declines which increases the amount of iron available for bacterial growth (31). The keratin plug sealing the teat breaks down about 7 to 10 d before parturition (23, 24), permitting bacteria easier access to the gland. At parturition, most dairy cattle become hypocalcemic (some to the point of developing milk fever) which is suspected to impair smooth muscle contraction vital to closure of the teat sphincter after milking. Why the immune system is depressed at parturition is currently unknown, although in another section of this review the possible effects of various endocrine and nutritional factors will be discussed.

- **Retained Placenta**

The fetal membrane villi should separate from the maternal caruncles within a few hours of calving. Numerous factors are thought to be important in determining whether the placenta is successfully expelled. Gross et al. (11) reported that injection of PGF2 within 1 h of calving dramatically reduced the incidence of retained placenta in dexamethasone-induced calvings, suggesting
that PGF2 production is deficient in cows developing retained fetal membranes. However, other researchers have not found prostaglandin treatment to be effective in prevention or treatment of retained fetal membranes (1, 29).

Numerous studies have been conducted to try to demonstrate a hormone deficiency or excess that is responsible for the retained fetal membrane syndrome, but no clear conclusions are evident (3). A great deal of epidemiological evidence exists that links milk fever with an increased incidence of retained fetal membranes (4). Presumably the hypocalcemia prevents uterine contractions necessary for expulsion of the placenta. While uterine contraction may be a factor in expulsion of the placenta in those cases in which the placenta is free of the caruncles, in most cases uterine contraction is actually stronger and more protracted in cows with retained placenta than in cows that expel the placenta normally (1).

Workers from the Netherlands are conducting studies, which suggest that the immune system plays a role in retained placenta. In a series of interesting experiments, Gunnink (12, 13) demonstrated that leukocytes (primarily lymphocytes) of cows that would expel the placenta normally had a strong chemotactic response to cotyledon material suspended in a Boyden chamber. In striking contrast, cows that failed to expel the placenta normally had peripheral blood leukocytes that exhibited little to no chemotaetraction to the cotyledon suspension. This inability to attack cotyledon material was evident several days before parturition in those cows that would develop a retained placenta. Gunnink proposes that placental tissue becomes a dead foreign body at the time of parturition, which the body must recognize and "reject" in order to complete separation of the fetal membranes. Perhaps immunosuppression at calving has implications for fetal membrane expulsion in addition to infectious disease susceptibility. In partial support of this theory, a loss in neutrophil chemotactic attraction for fetal membrane tissue after parturition, but not before, has also been observed (2) in cows with retained fetal membranes. These workers also reported that neutrophil superoxide production was impaired before calving in those cows that would develop metritis after calving. One Dutch study (17) suggests that retained placenta is more likely to occur in those pregnancies where the fetus has the same major histocompatibility complex antigens (MHC class I) as the cow. Since MHC class I antigens are important in recognition of "self" antigens these studies suggest that failure to recognize the placenta as foreign can increase the incidence of retained placenta. Could inbreeding, common in dairy cattle, be a factor contributing to retained placenta?

When parturition is induced with glucocorticoids it is often accompanied by retained placenta. Milk fever cows have several fold higher plasma cortisol concentrations at calving than do non-milk fever cows. Could the immunosuppressive effects of the glucocorticoids be the reason for the higher incidence of retained placenta in these two situations?
Endocrine and Nutritional Influences on Periparturient Immunosuppression

Estrogens, which increase dramatically at the end of gestation, have been found in some experiments to stimulate the humoral immune response (32), but most workers agree they have a strong suppressive effect on cell-mediated immunity (35). Glucocorticoids have long been used as powerful immunosuppressive agents. Plasma cortisol concentrations (primarily of maternal adrenal origin) of the cow increase from 4 to 8 ng/ml 3 d before calving to 15 to 30 ng/ml at parturition and the d after calving. The cortisol secretion response is even more pronounced in those cows that develop milk fever (9). Thus, the immunosuppressive effects of the plasma estrogen and cortisol increases observed in the periparturient period would be likely suspects as causative agents of the immunosuppression observed at calving.

Chronic deficiencies of energy, protein, minerals, or vitamins have repeatedly been associated with increased disease susceptibility as a result of depressed immune function. Parturition and the onset of lactation impose a large metabolic stress on the cow, which can cause relatively acute, lasting from 1 d to several wk, deficiencies of nutritional factors necessary for maintenance of the immune system. Partly because of the poor development of the digestive tract, it is impossible for the high producing dairy cow to ingest enough feed to meet the lactational demands for energy and protein. Therefore, the dairy cow is in negative energy and protein balance in early lactation, which impairs immune function.

Severe energy deficiency in early lactation can also cause ketoacids to accumulate in the blood, which can further impair lymphocyte function (7). Plasma concentrations of vitamin A (retinol) and vitamin E (tocopherol) were found to decrease 38% and 47%, respectively, in dairy cows at parturition (10), which caused plasma levels of these vitamins to fall to levels that would be diagnostic of chronic deficiency. While a portion of the serum loss of these vitamins may be due to sequestration within colostrum, it also appears that they are being consumed at a higher rate at calving as a result of increased immunologic and metabolic stress. Vitamin A and vitamin E supplementation in the periparturient cow can improve immune responses (5, 14, 25, 28, 30), and is often associated with a decrease in the incidence of mastitis in dairy cows (25, 26). A point to be made here is that the vitamin and mineral requirements of the cow have generally not been determined for the periparturient cows, and that these requirements appear to be considerably higher than would be predicted from data obtained in cows outside this time frame. It would seem logical to conclude that any nutritional insults to the immune system would add to the immunosuppression caused by the hormonal changes associated with parturition.
Maintaining a strong immune system

At calving all cows white blood cells show a decreased ability to fight off infections which increases the susceptibility to mastitis and uterine infections. In part the immune suppression is thought to be due to changes in hormones at calving. However better nutrition can also strengthen the immune system at this time. How do we do this?

Prevent energy and protein deficiency

- The effect of energy deficit on the immune function is, in my opinion, greatly underrated!

Feed adequate selenium

- 0.3 ppm is legal limit in USA. In some situations this is not enough!
- Injectable selenium may be an option.

Feed vitamin E to animals without access to pasture.

- Recent work (34) suggesting that adequate vitamin E may require 4000 IU / day for the 2 weeks before calving and 2000 IU / day after calving. This work was done feeding 0.1 ppm selenium causing the authors to be cautious in their recommendations. I believe that the results would be the same even if selenium had been adequate. Much higher than NRC suggests!
- Recommendation - 2000 IU vitamin E / day for last 2-3 weeks of gestation, 1000 IU / day for first weeks of lactation. Pastured animals require no supplemental vitamin E.
- Expensive, but worth it if it prevents just one case of mastitis per 100 cows.
- Injectable vitamin E is an option also. 3-5 g subcutaneously 30 days before calving and again within a week of calving. Occasional abscess at injection site when given intramuscularly!

Prevent milk fever

- Milk fever causes tremendous release of cortisol which inactivates the immune cells

Supply trace minerals at 20 - 50% above NRC recommendations

- This will account for decline in dry matter intake that accompanies calving.
Copper and zinc deficiency seem to be the problems we see most in Midwest -often caused by too much iron in the ration and the water!

**Payoff** - Less mastitis, retained placenta (enhancement of neutrophil attack on fetal tissues!) and uterine infection.

**References**